Tetrahedron Letters 60 (2019) 513–523

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Progress in intermolecular and intramolecular reactions of thioamides with diazo compounds and azides

Vasiliy Bakulev [a,*], Yuri Shafran [a], Wim Dehaen [b]

[a] Ural Federal University named after the first President of Russia B.N. Yeltsin, 19 Mira str., 620002 Yekaterinburg, Russia
[b] Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium

ARTICLE INFO

Article history:
Received 19 September 2018
Revised 31 December 2018
Accepted 16 January 2019
Available online 17 January 2019

Keywords:
Thiazoles
Thiophenes
Tetrazoles
Enaminones
Amidines

ABSTRACT

Reactions of thioamides with nitrogen-rich 1,3-dipoles, diazo compounds and azides, have been known for long time already. However in recent years introduction of catalysts of different types (rhodium-, ruthenium- and copper-containing and Lewis acids) as well as highly electrophilic sulfonyl azides, allowed the development of new methods for the synthesis of heterocycles, enamines and *N*-sulfonyl amidines. Moreover, a new methodology in organic synthesis, based on generation and subsequent transformations of α-diazocarbonyl compounds was created. Reactions of sulfonyl azides with thioamides undergo readily in mild conditions to produce different sorts of *N*-sulfonyl amidines and represent a new type of click-type processes. Most of the cited works were published in the current decade. Earlier seminal papers are also reviewed when they constitute the background for new synthetic methods which were developed further.

Contents

Introduction

Thioamides exhibit wide range of biological properties such as antifungal [1], antioxidant [2,3] and anticonvulsant [4] activities. Some of them strongly inhibit phosphoglycerate dehydrogenase [5]. Furthermore they also have found wide applications as intermediates in organic synthesis for the preparation of heterocycles and many valuable organic building-blocks [6–9]. The chemical properties of thioamides are considered in a review from Jagodzinski [6] in 2003 and by Dyachenko *et al.* [7] in 2018. We have turned our attention to data on catalytic and thermal reactions of thioamides with diazo compounds and with sulfonyl azides, information, that these reviews did not contain, apart of a few examples. At the same time these reactions represent new and effective methods for the synthesis of various heterocyclic compounds, new types of amidines and their vinylogs, enamines [10,11], exhibiting various types of biological activity [10], and can be used in synthetic organic chemistry as valuable chemical reagents [8,9]. In this digest, we have summarized the literature reports on the progress in synthetic methods and in reactions of thioamides with diazo compounds and azides including thermal and catalytic processes.

Synthesis of thioamides

The main methods of the synthesis of thioamides include: (i) Thionation of amides with P_4S_{10} [11a], with complex of P_4S_{10}

* Corresponding author. Tel.: +7-343-374-5483; fax: +7-343-375-4135.
E-mail address: v.a.bakulev@urfu.ru (V. Bakulev).

https://doi.org/10.1016/j.tetlet.2019.01.032
0040-4039/

with pyridine in organic solvents [11b] or in the presence of hexamethyldisiloxane [11c], with the system of $PSCl_3/H_2O/Et_3N$ [11d] and with Lawesson's reagent [11e], (ii) reaction of nitriles with H_2S or its precursors in the presence of bases [11f], (iii) Wilgerodt-Kindler reaction, including three-component reactions [11 g,h,i], basic and metal-catalyzed variants [11 g,h,i], (iv) reactions of aromatic and heteroaromatic compounds with isothiocyanates in the presence of Lewis acids [8].

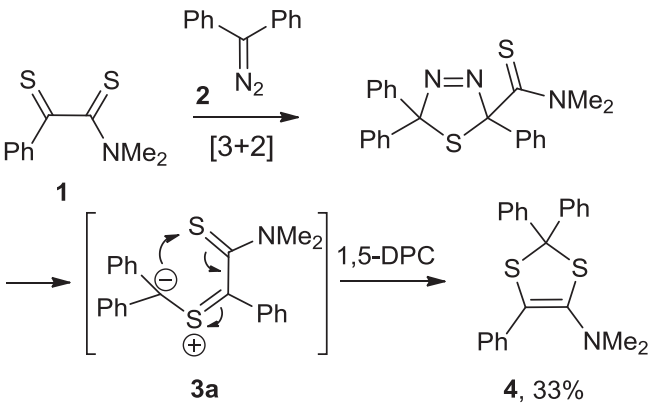
Reactions of thioamides with diazo compounds

Thermal reactions. In contrast to the cycloaddition reactions of thioketones [12–15], the analogous reactions of thioamides are scarce [16,17]. Careful study of reaction of 2-thiocarbonylthioamides **1** with diphenyl diazomethane **2** undertaken by the Heimgartner group has shown that the thioamide moiety did not take part in cycloaddition reaction but participated in subsequent 1,5-dipolar electrocyclization of thiocarbamoyl thiocarbonyl ylides **3a** formed in reaction of thioketone group with compound **2** to afford dithiole **4** in 33% yield (Scheme 1) [16].

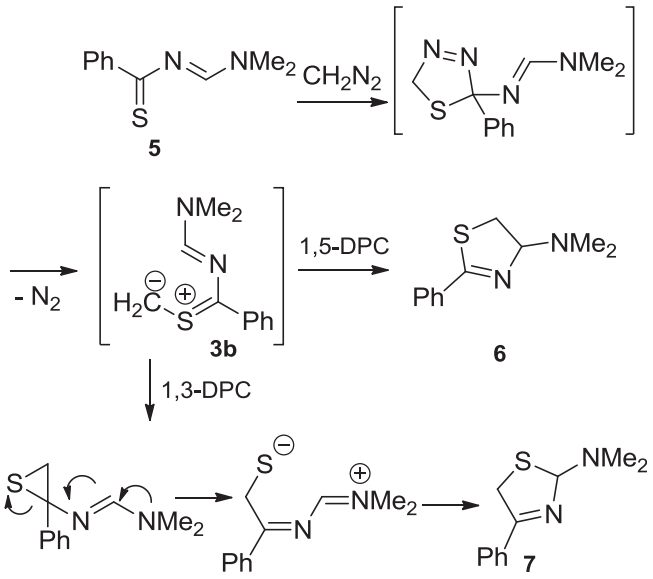
Heimgartner and coworkers have shown that *N*-methylidene thioamides **5**, where the C=S bond is conjugated with N=C, are more reactive than thioamides with an adjacent amino group. This reaction is interesting from a theoretical point of view providing evidence that the disruption of thioamide resonance increases the reactivity of the C=S bond toward a diazo group. Thioamide **5** reacted with diazoalkane *via* intermediate thiocarbonyl ylide **3b** to form a mixture of 2,5- and 4,5-dihydrothiazoles **6** and **7** in moderate yields [17]. The formation of two types of products was explained by competition between 1,5- and 1,3-electrocyclic reactions of thiocarbonyl ylide **3** leading to **6** and **7** respectively (Scheme 2).

Alkyl and aryl carbothioamides **8** have been shown to react with ethyl diazopyruvate in the presence of boron trifluoride etherate affording 2-substituted 4-carbethoxythiazoles **9** in good yields (Scheme 3) [18].

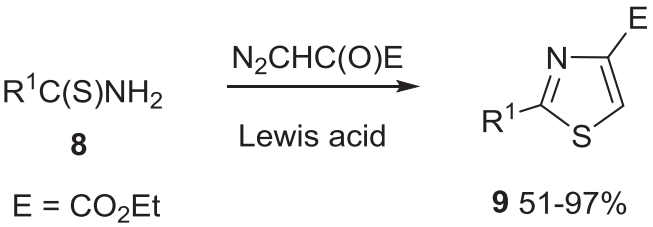
Cyanothioformanilide has been shown to exhibit very high reactivity towards diphenyl diazo methane **2** to form α-cyano-β, β′-diphenylenamine **10**, in the absence of any catalyst and additives, in 40% yield. It is the first and single example of the synthesis of enamines by reaction of thioamides and diazo compounds. The reaction takes place under very mild conditions and is completed in 25 min at room temperature. A plausible mechanism includes the formation of thiadiazoline **11** and thiirane **12** intermediates similar to those in reactions of thioketones with diazoalkanes (Scheme 4) [19]. *Metal-catalyzed reactions.* Thermal reactions of thioamides with diazo compounds are limited to a few examples of the synthesis of thiazoles, completing the Hantzsch synthesis.



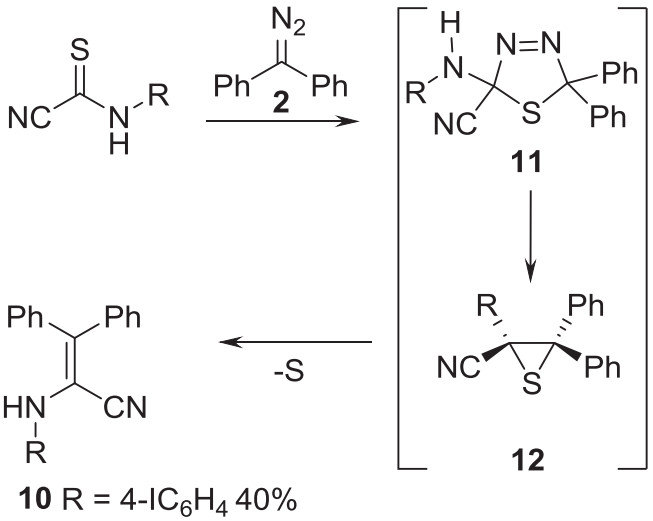
Scheme 1. Synthesis of dithiole **4**.



Scheme 2. Reactions of thioamides **5** with diazomethane.



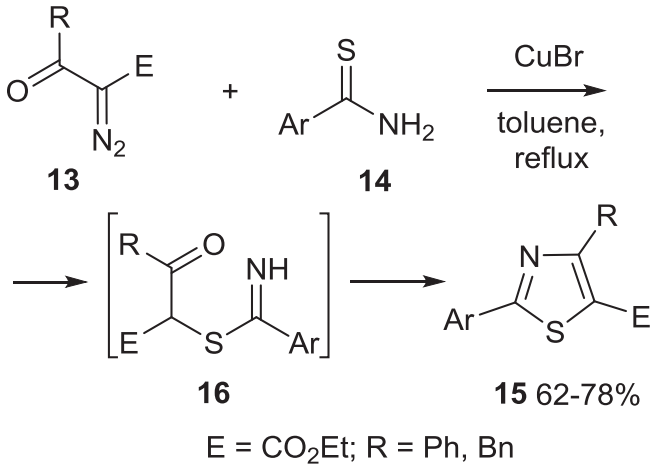
Scheme 3. Synthesis of thiazoles **9**.



Scheme 4. Synthesis of enamines **10**.

This section includes data on the synthesis of thiazoles, thioisomunchone, benzothiazine, thiophenes and enaminones by reactions of thioamides with diazo compounds in the presence of rhodium-, ruthenium- and copper-containing catalysts.

Thiazoles. Villagordo *et al.* have found that diazoketoesters **13** react readily with primary thioamides **14** under reflux in toluene in the presence of copper bromide to afford 2,4,5-trisubstituted thiazoles **15** in 60–80% yields (Scheme 5) [20]. The fact that the



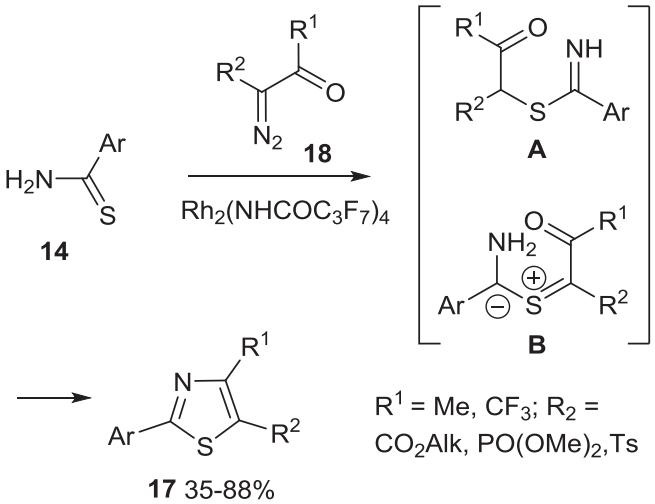
Scheme 5. Synthesis of thiazoles **5**.

catalyst was used in equimolar amount was the reason to propose a mechanism where thioimidate **16** was the key intermediate of the process. Notably, thioamides of aliphatic acids also react in these conditions to form similar products but in lower yields.

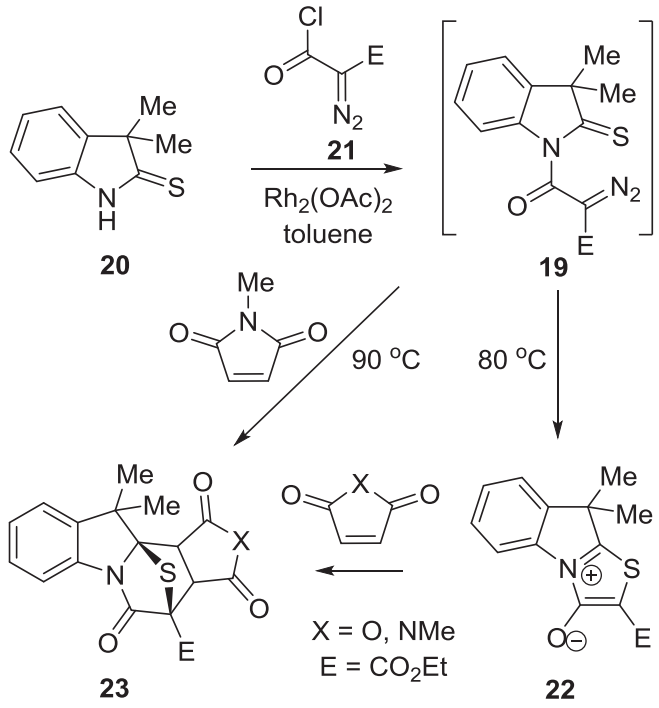
Moody and coworkers demonstrated the use of $Rh_2(NHCOC_3F_7)_4$ to prepare a series of thiazoles **17**, bearing various aryl substituents in position 2, and carboxylate, phosphonate or tosyl groups in position 5 of the ring, in 35–88% yield [21]. The authors considered two alternative mechanisms **A** and **B** for this reaction. The first is similar to work of Villagordo *et al.* [20] and involves the insertion of a carbene into the SH bond of the thioamide – imino tautomer to give thioimidate **A**. The second one more likely includes the formation of a thiocarbonyl ylide **B** as a key intermediate (Scheme 6) [21,22]. No arguments in favor of the mechanism **B** were given.

Intramolecular interaction of diazo and thiocarbonyl functions was observed in rhodium tetraacetate-assisted cyclization of diazo-thione **19** generated from indoline-2-thione **20** and diazo compound **21** to form thioisomunchnone **22**. The latter is a masked thiocarbonyl ylide which can react with *N*-methylmaleimide and maleic anhydride to afford cycloadducts **23** (Scheme 7) [23].

Benzothiazines. The Reddy group has discovered the formation of a thiazine ring as a result of the copper-catalyzed reaction of thioamides bearing the diazoester moiety **24** in the molecule. This



Scheme 6. Reaction of thioamide **14** with diazo compounds **18**.

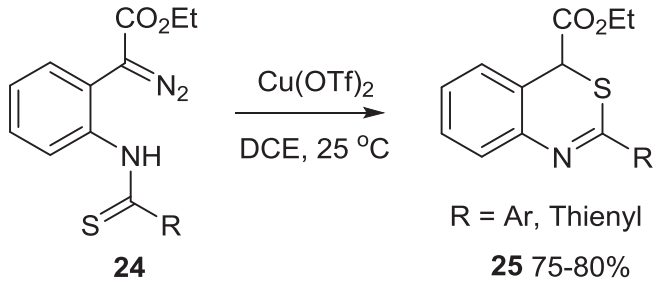


Scheme 7. Synthesis of thioisomunchnone **22** and its cycloadducts **23**.

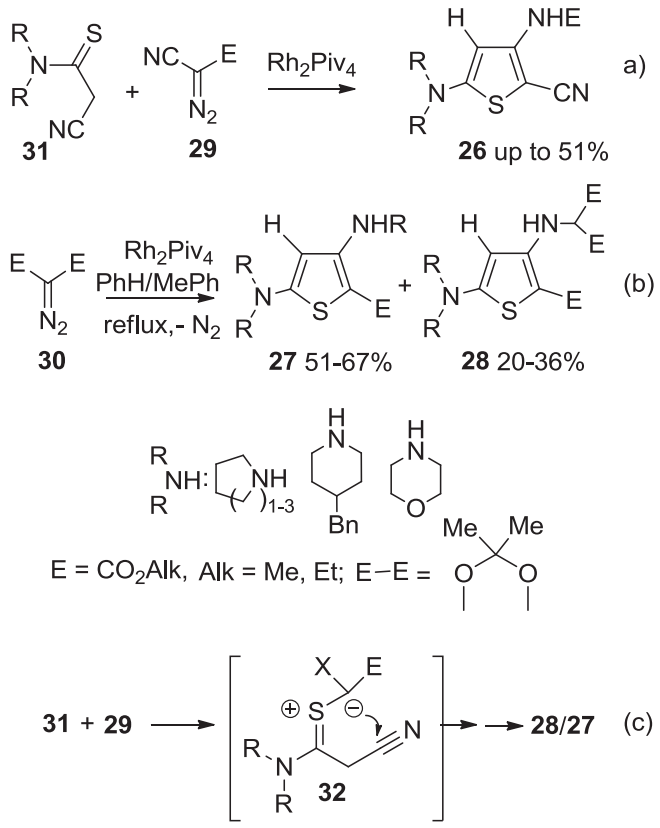
furnished a small series of benzo[*d*][1,3]-thiazines **25** in 75–80% yields. A plausible mechanism involves the insertion of a copper carbenoid into the thiocarbonyl group, leading to the formation of a thiocarbonyl ylide followed by an H-shift which finalizes the process (Scheme 8) [24].

Thiophenes. Jointly with the Nikolaev group we have developed a method for the synthesis of 2,3,5-trisubstituted thiophenes **26**, **27** and **28** based on Rh(II)-catalyzed reactions of 2-diazo-2-cyanoacetic **29** and 2-diazo-malonic esters **30** with tertiary 2-cyanothioacetamides **31** in 52–97% yields (Scheme 9). A possible mechanism involves the formation of thiocarbonyl ylide **32**, intramolecular cyclization of the negatively charged carbon atom of the latter onto the cyano group followed by H and ester shifts to give thiophenes **27/28** (Scheme 9) [14]. The formation of unexpected products **28**, occurring only in the reaction of 2-diazomalonic esters, was explained by saponification of ester group followed by decarboxylation to form 4-aminothiophene **27** (R = H) and insertion of a carbenoid derived from diazomalonic esters **30** into the amino group of aminothiophene [25].

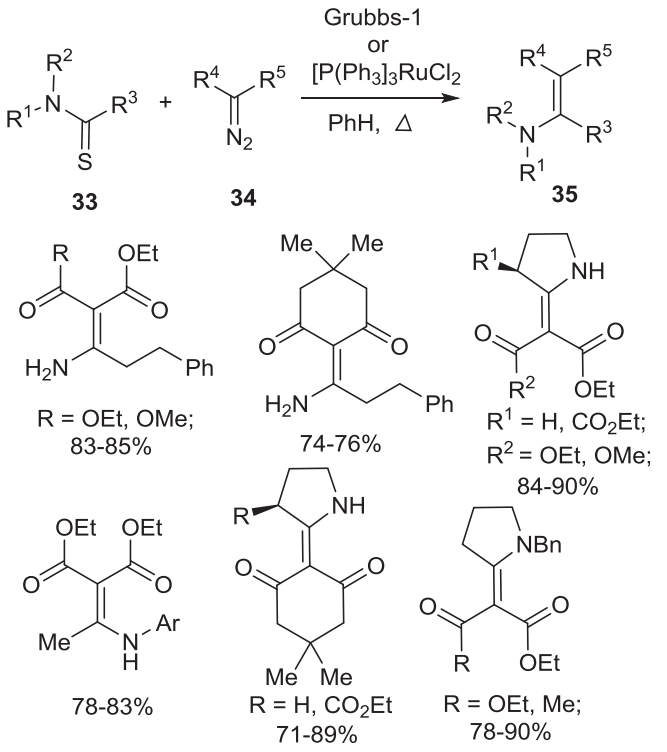
Enaminones. In their earlier publications, the Padwa and Danishefsky groups used the rhodium-catalyzed reaction of thioamides with diazocarbonyl compounds in the synthesis of indolizomycin [26] and thioisomunchnones [27]. Subsequently, Nakano and co-workers [28] have reported the formation of a



Scheme 8. Synthesis of thiazine **25**.



Scheme 9. Reaction of thioacetamides **31** with compounds **29/30**.



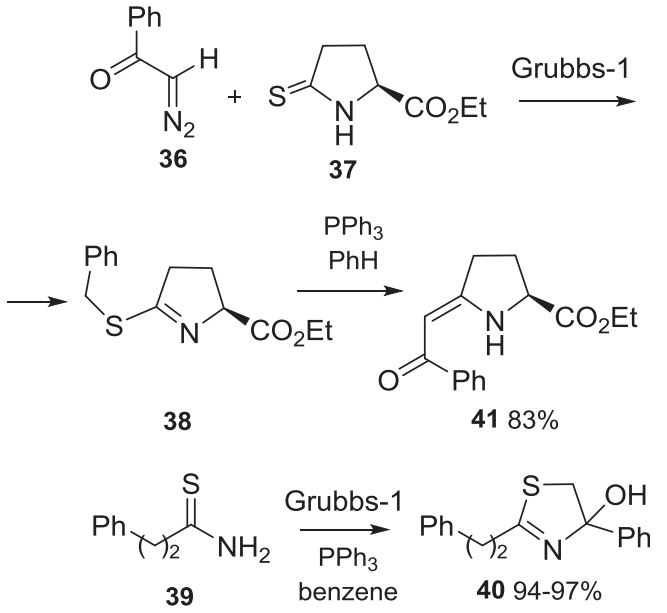
Scheme 10. Selected examples of reactions of thioamides **33** with diazo compounds **34**.

mixture of thioimidates and enaminones as a result of the reaction of diazoesters with thiobenzamides.

Until 2012, there were only two publications where the rhodium-catalyzed variants were used in intermolecular reactions [26,28]. Recent trends in the progress of reaction of this type dealt with the use of ruthenium- [29–31] and copper-containing catalysts [32,33]. A systematic study was made by Hussaini and coworkers, who have discovered and carefully studied intermolecular reactions of primary, secondary and tertiary thioamides with diazoketones and diazoesters in the presence of seven types of ruthenium catalysts [29–31]. They have found that the reaction of thioamides **33** with diazo dicarbonyl compounds such as diazoesters, diazoketoesters and diazoketones **34** takes place readily in a sealed tube at 120 °C in the presence of ruthenium catalysts, Grubbs-1 or $[PPh_3]_3RuCl_2$ to furnish enaminones **35** in good yields. Because of dimerization of diazo compounds, two equivalents of diazo compounds are required to complete their reactions with *N*-benzylthiopyrrolidine (Scheme 10).

In optimal conditions, the reaction of diazoacetophenone **36** with thioamide **37** follows another course to give iminothioether **38** as the main product. It is worth mentioning that the direction of the reaction of thioamides with diazoketones depends on whether primary **39** or secondary thioamides were used leading to 3-hydroxy-thiazolines **40** or thioimidates **38**, respectively. The use of triphenylphosphine as an additive in the reaction of secondary thioamides **37** allows to convert **38** to *Z*-enamine **41** in 83% yield (Scheme 11) [29].

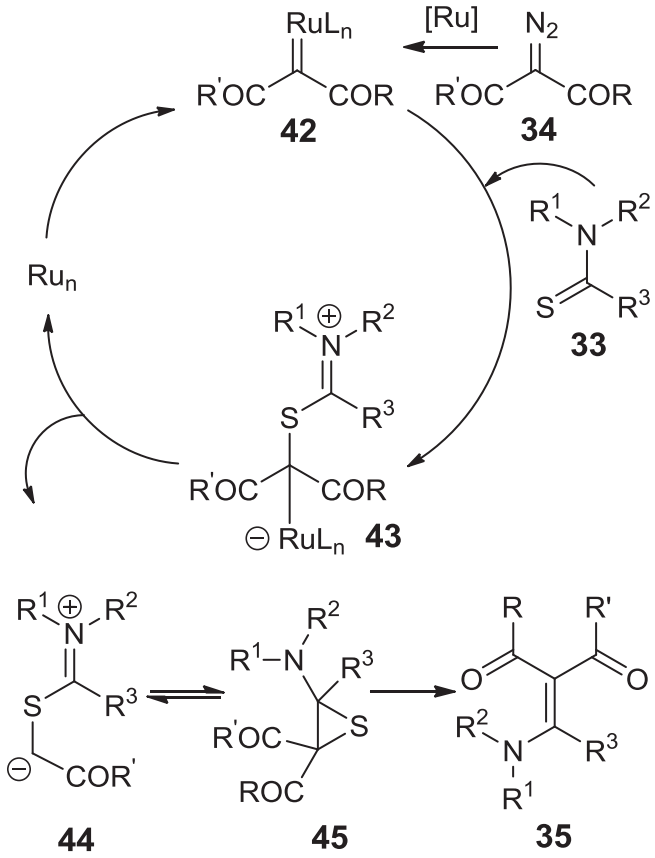
The proposed mechanism of enaminone **35** formation includes the formation of ruthenium carbene **42**, followed by the attack of the latter onto the sulfur atom of thioamides **28** to form ruthenium complex **43** and, after release of the catalyst, the formation of thiocarbonyl ylide **44** (Scheme 12) [29]. The latter, *via* 1,3-electrocyclic



Scheme 11. Synthesis of enamines **41** and thiazoles **40**.

reaction, forms thiirane **45** and elimination of sulfur gives rise to the final product, enaminone **35**.

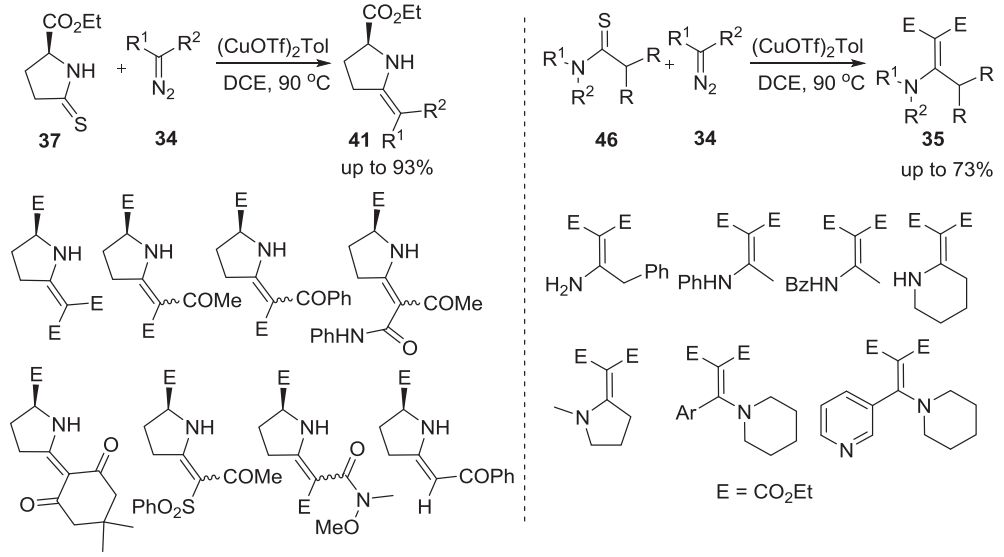
The Hussaini group has improved the synthesis of enaminones from thioamides based on the copper-catalyzed reactions of diazo carbonyl compounds [20]. They have found that the use of $(CuOTf)_2Tol$ in dichloroethane at 90 °C is the method of choice for the synthesis of enaminones **41** or **35** by reactions of thioamides **37** or **46** with various types of diazo compounds **34** (Schemes 13) [31].



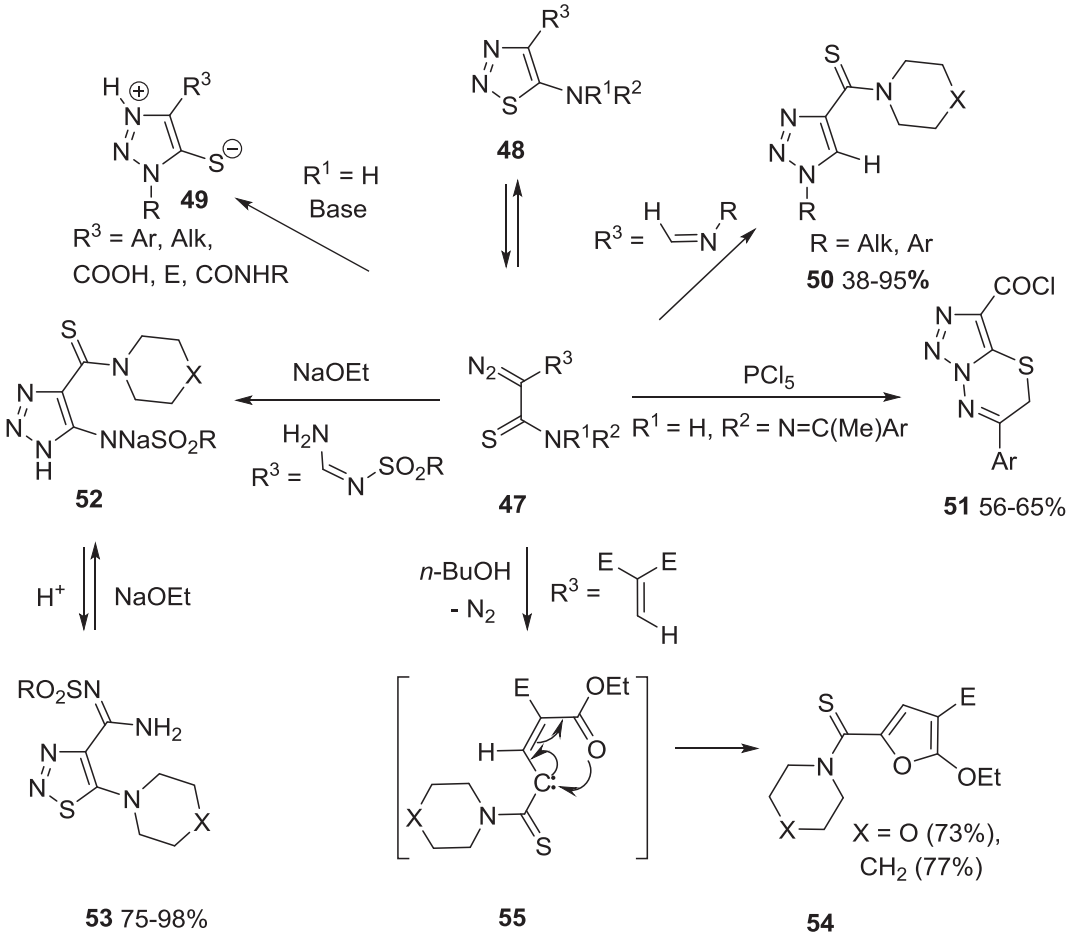
Scheme 12. Plausible mechanism of synthesis of enaminones **35**.

The reaction has broad scope and tolerates variations of structures of both starting reagents, diazo compounds and thioamides. Thus, 2-diazomalonic ester, 2-diazo-2-acetyl(benzoyl)acetic ester, 2-diazoketones, 2-diazo-2-phenylsulphonylacetone, diazo compounds bearing various amide groups and diazo acetophenone were used in reactions with primary, secondary and tertiary thioamides to afford a variety of enaminones, predominantly in very good yields. Contrary to the reactions in the presence of Rh and Ru catalysts, no dimers of diazo compounds or thioimidates were observed. The authors have shown that reaction of thioamide **37** with diazo compounds **34** bearing different R^1 and R^2 occurs in most cases diastereoselectively with d.e. from 1:1 to 17:1. This selectivity was explained by the higher stability of Z-isomer. The formation of the products of insertion in NH and CH bonds does not occur. A plausible mechanism for formation of enamines proposed by the authors is similar to that proposed by Hussani *et al.* for the reaction catalyzed by a ruthenium catalyst [30]. Further improvement of the approach to enaminones by copper-catalyzed reaction of diazo compounds with thioamide was made by the Hussaini group by the use of a copper(I)-complexed magnetic nanoparticle catalyst. The catalyst reduces the time of reaction, decreases its temperature and provides high yields of a series of enaminones [32].

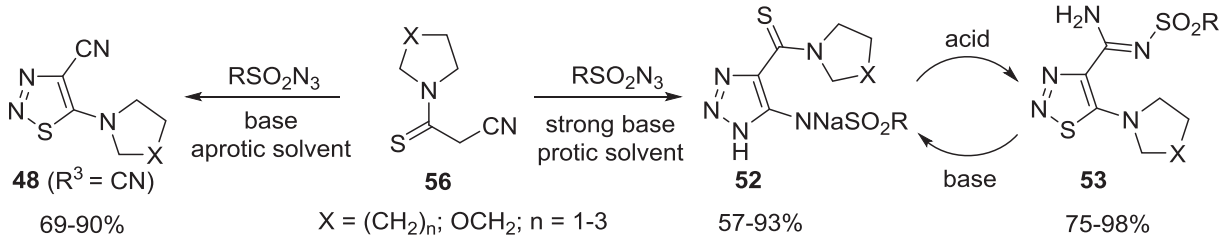
Transformations of α-diazothioacetamides. The cyclization of α-diazothiocarbonyl compounds **47** occur as a very fast 1,5-electrocyclic reaction to form relatively stable 1,2,3-thiadiazoles **48** (Scheme 14) [34,35]. The theoretical and experimental study of this and similar electrocyclic reactions have shown them to proceed with very low barriers which led to the concept of heteroelectrocyclic [36] or pseudopericyclic [37] reactions. Because the cyclization of diazothiocarbonyl compounds is straightforward to 1,2,3-thiadiazoles, the methods of the synthesis of the latter are based on the syntheses involving unstable diazothiones [34,35]. The three general methods leading to compounds **48** include the diazo group transfer [34,35,38] onto active methylene thioamides with sulfonyl azides, diazotization of amines bearing thiocarbamoyl group and rearrangements of 1,2,3-triazole-4-carbothioamides [35]. 1,2,3-Thiadiazoles are prone to transformations and rearrangements taking place via α-diazothiones as shown in Scheme 15. Thus thiadiazoles **48** undergo Dimroth-type rearrangement to form 1*H*-1,2,3-triazol-3-ium-5-thiolates **49**, in good yields [34]. 4-Carbimino-1,2,3-thiadiazoles **48** (R^3 = HC = NR) formed by reaction of 4-formyl-1,2,3-thiadiazole with amines, are labile and rearrange to 1,2,3-triazol-4-carbothioamides **50** under the conditions used for their generation [39,40]. It was found that interaction of 1,2,3-thiadiazolylhydrazones of acetophenones with phosphorus pentachloride in benzene or toluene leads to 5*H*-[1,2,3]triazolo[5,1-b][1,3,4] thiadiazines **51**. The reaction most likely involves Dimroth-type rearrangement of the thiadiazole ring into a triazole followed by intramolecular cyclization of Me and SH groups after treatment with PCl_5 [41].



Scheme 13. Copper-catalyzed reactions of thioamides **37** and **46** with diazo carbonyl compounds **34**.



Scheme 14. Rich chemistry of α-diazothioacetamides **47**.



Scheme 15. Three directions of cyclization of 2-cyanothioacetamides with sulfonyl azides.

Recently, we have prepared a series of 5-sulfonylamido-1,2,3-triazoles as sodium salts **52** by reaction of tertiary 2-cyanothioacetamides **56** with various arylsulfonyl azides in very good yields (Schemes 14 and 15) [42,43]. The proposed mechanism involves the cyclization of diazo compounds **47** bearing thiocarbonyl and imidamide groups to triazoles **52**. Careful studies have shown that the reaction occurs *via* three pathways to furnish generally a mixture of 5-amino-4-cyano-1,2,3-thiadiazoles of type **48** (R^3 = CN), 5-sulfonylamido-1,2,3-triazole-4-carbothioamides **52** and 5-amino-1,2,3-thiadiazole-4-carboximidamides **53** (Scheme 15**)**. Optimizing the reaction, we managed to find conditions for the synthesis of each compound as a single product. Amidino-thiadiazoles **53** were prepared by rearrangement of triazole **52** occurring in dilute hydrochloric acid [42]. Interestingly, reactions of tertiary cyanothioacetamides **56** with highly electrophilic 5-azido-1-methyl-4-nitroimidazole led to thiadiazole of type **53** (R = 1-methyl-4-nitroimidazol-5-yl) [44].

The first example of transformation of 1,2,3-thiadiazoles *via* carbene intermediate was observed in 2006 by the Morzherin group when a 1,2,3-thiadiazole bearing an ethoxycarbonylvinyl group in position **48** was refluxed in *n*-butanol causing the loss of N_2 from the intermediate diazo compound **47** to afford 5-ethoxyfurans **54** *via* carbene **55** (Scheme 14) [45]. Ten years later, Gevorgyan and Kurandina [46] and subsequently the Lee group [47–49] have undertaken rhodium-catalyzed reactions of 1,2,3-thiadiazoles with alkenes, alkynes and nitriles, including the intramolecular mode, that confirms the existence of an equilibrium between 1,2,3-thiadiazole **48** and its open chain isomer, diazo thioacetamide **47** (Scheme 14).

Reactions of thioamides with azides

This section is organized according to the type of product obtained.

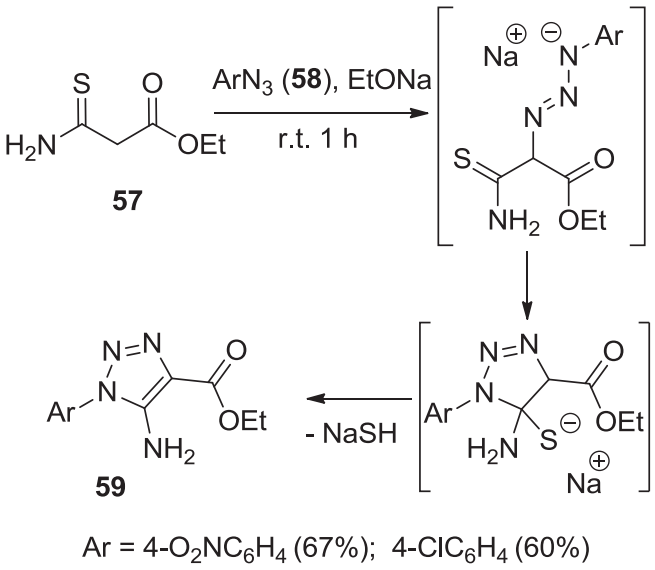
1,2,3-Triazoles. Primary thioamide **57** was first found to undergo cyclization upon action of aryl azides **58** in ethanolic sodium ethoxide into ethyl 5-amino-1-phenyl-1,2,3-triazole-4-carboxylates **59** *via* a Dimroth reaction mechanism (Scheme 16) [43].

Tetrazoles. In recent years, the synthesis of tetrazoles from thioamides and azides was much improved by introducing new azidation systems that include catalysts and additives. Thus, primary aliphatic and aromatic, secondary acyclic, cyclic, and heterocyclic thioamides **60** undergo 'unprecedented high-yield simple and mild conversion' into 5-substituted, 1,5-disubstituted, or annulated tetrazoles **61**, on treatment with a $SiCl_4/NaN_3$ reagent system in refluxing acetonitrile (Scheme 17). The authors evidenced the mechanism of activation of C=S bond by its interaction with $SiCl_4$ to form thioimidate **62** by isolating *N*-silyl triazoles **64** (when primary thioamides are put into the reaction). The cyclization of azidoimine **63** formed in reaction of thioimidate **62** with sodium azide to intermediate tetrazole **64** followed by hydrolysis of the latter are final steps in the synthesis of tetrazoles **61** [50].

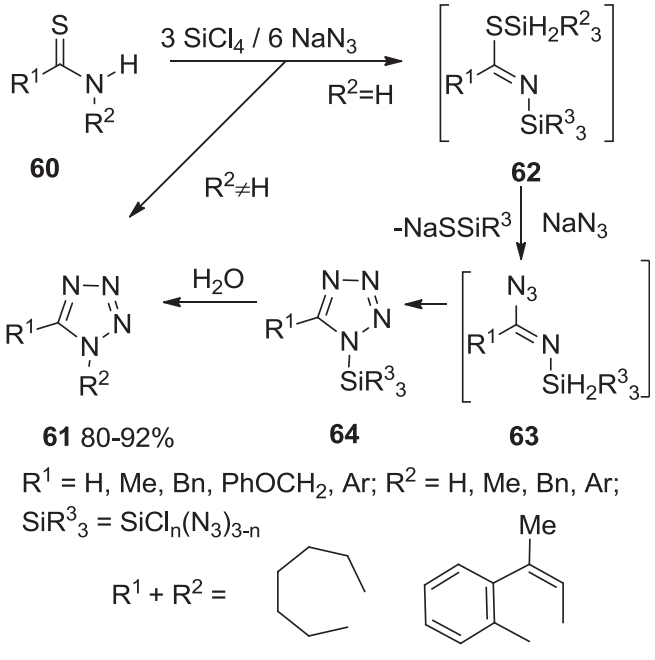
Another azidation system, trimethylsilylacetylene (TMSA)/triphenylphosphine (TPP)/diisopropyl azodicarboxylate (DIAD), was also used to prepare several tetrazoles **65** including bis tetrazoles, from linear N^{α},N^{ω}-ditritylated polyamino mono- or bisthioamides **66** (Scheme 18) [51].

The same azidation system was applied to prepare 5-(4-(1,2-dithiolan-3-yl)butyl)-1-(3,4-dimethoxyphenethyl)-1*H*-tetrazole **67a** in good yield from thioamide **68a** (Scheme 19) [52]. The synthesis of tetrazoles **67a-e** was carried out in order to explore the influence of the bioisosteric replacement of the amide group on the neuroprotective activity of the lipoic acid/dopamine conjugate (Scheme 19) Thioamides with similar structures **68b** and **68c** in the same reaction conditions afforded tetrazoles **67b** and **67c** in drastically different yields (100% and 47%, resp.) while the starting and resulting compounds differ only in the number of methylene chains in the linker between NH and 3,4-dihydro-benzopyrane [53]. No rationale is given to the observed phenomenon. Tetrazoles **67d,e**, comprising both 5-(4-(1,2-dithiolan-3-yl)butyl) (as in [52]) and 1-(3,4-dihydro-6-methoxy-2,2,7,8-tetramethyl-2*H*-1-benzopyran-5-yl-methyl) (as in [53]) moieties were reported in the paper [54]. Here again, the same correlation between the length of the linker in starting thioamides **68d,e** and the yield of tetrazoles **67d,e** was observed and left undiscussed.

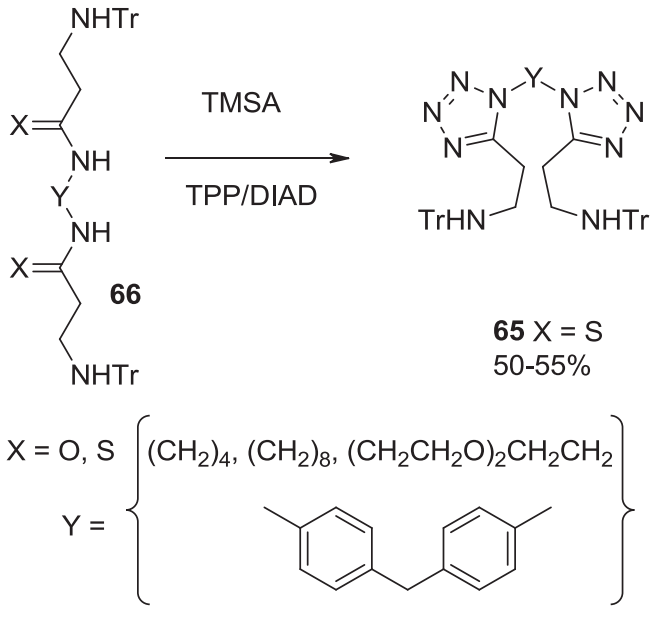
In the search for new P2X7 antagonists among tetrazole derivatives, the investigators [55,56] have synthesized tetrazoles **69** from thioamides **70** with TMSA in the presence of mercury(II) salts (Scheme 20). A small variations of the method involves addition of a base and triethylamine, to the reaction mixture [55]. Neither the data within the paper [55] nor comparison with reactions described in the other sources [57,58] could be used to deduce the role of triethylamine in the process. The yield of a representative tetrazole **69** (R^1, R^2 = Cl, H) prepared by the researchers from Abbott Laboratories [55] was unusually high (95%). The use of mercury(II) acetate was advantageous in one more synthesis from thioamide **70** (R^1 = 6-methoxycarbonyl-imidazo[1,2-*a*]pyridin-8-yl, R^2 = CHF_2) [57]: the yield of the corresponding tetrazole **69** was as high as 97% (Scheme 20). Catalysis with mercury(II) acetate



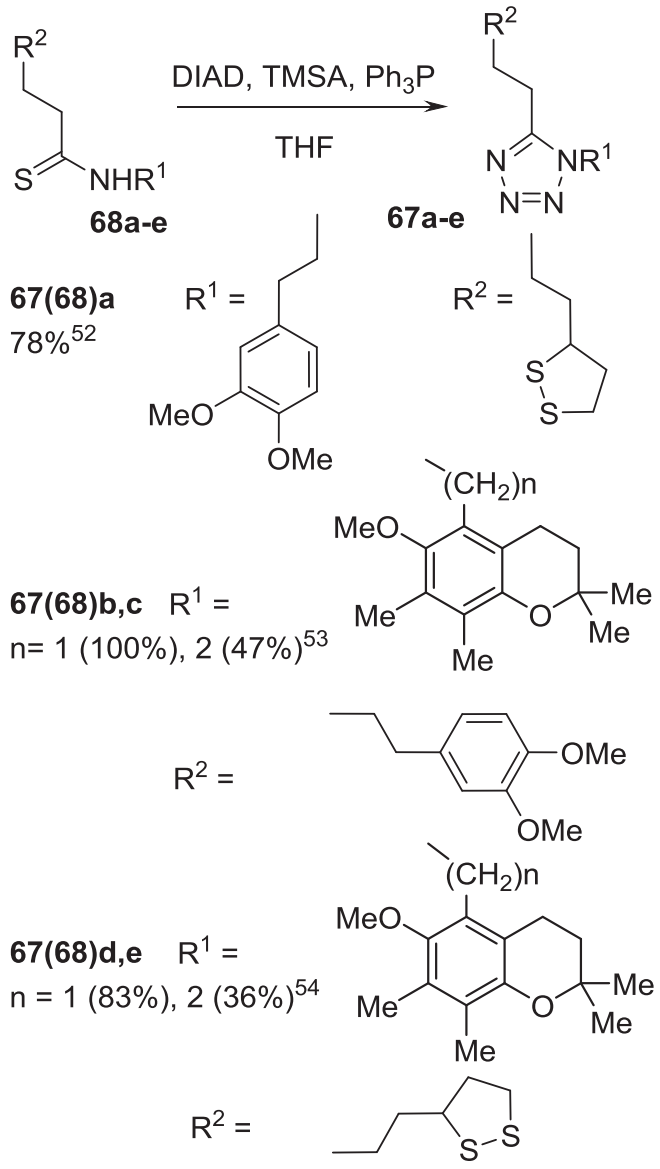
Scheme 16. Synthesis of triazoles from primary thioamides **57** and aryl azides **58**.



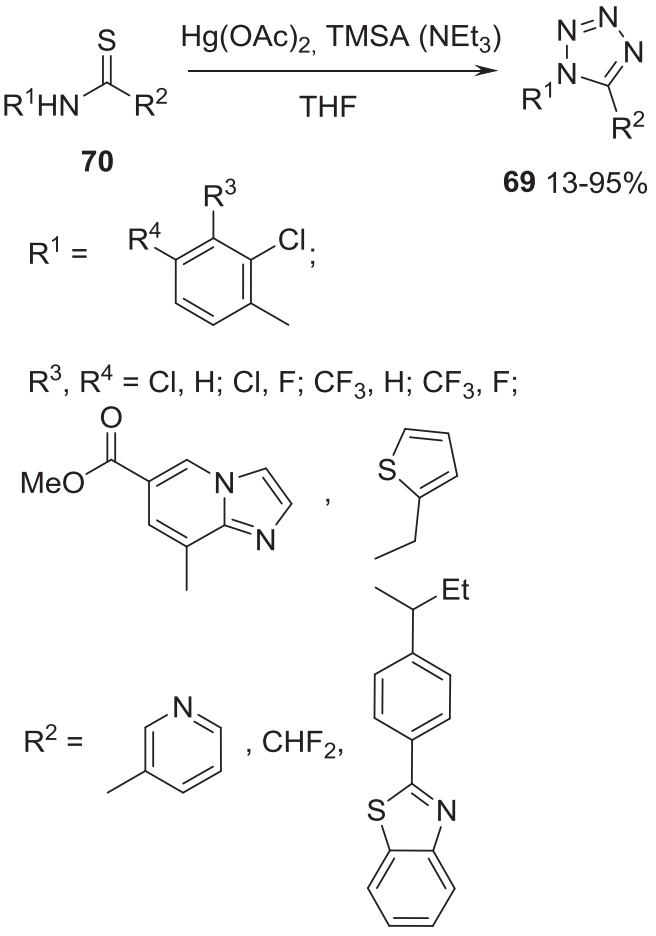
Scheme 17. Synthesis of tetrazoles **61.**



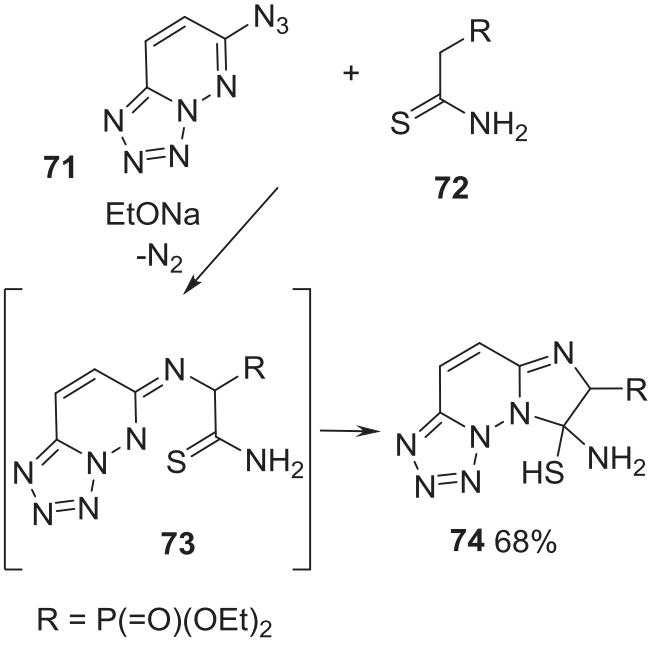
Scheme 18. Synthesis of tetrazoles **65**.



Scheme 19. The synthesis of tetrazoles **67**.



Scheme 20. Synthesis of tetrazoles **70**.



Scheme 21. Cyclization of thioamide **72** with azide **71**.

is not a guarantee of success: the yield of tetrazole **69** (R^1 = (2-thiophene)methyl, R^2 = 1-[4′-(benzo[*d*]thiazole-2-yl)phenyl]prop-1-yl) was disappointingly low (13%) (Scheme 20) [58]. Anyway, there remains a concern that the use of toxic mercury-containing compounds conflicts with the current trend of applying more eco-friendly techniques.

TMSA/DCM/$FeCl_3$ [59] and the metal scavenger Smopex®-301 (styryl diphenylphosphine grafted polyolefin fiber) [60] were applied for the synthesis of a sterically rich tetrazole and 1-benzyl-5-(hex-5-enyl)-1*H*-tetrazole respectively.

Dihydroimidazole. A unique reaction, where the reacting center in the thioamide counterpart is neither C═S nor C-NH_2 bond but a central C atom, is the cyclization of 3,6-diazidopyridazine **71** with diethyl (2-amino-2-thioxoethyl)phosphonate (**72**) in the presence of EtONa (Scheme 21) [61]. The authors postulate the intermediacy of the tetrazolopyrazine **73** resulting from the attack of the nitrene that could be formed from the azide **71**, onto the CH_2 in phosphonate **72**. However, the structure of the resulting 7,8-dihydroimidazo[1,2-*f*]tetrazolo[1,5-b]pyridazine **74** has not been 100% reliably proved.

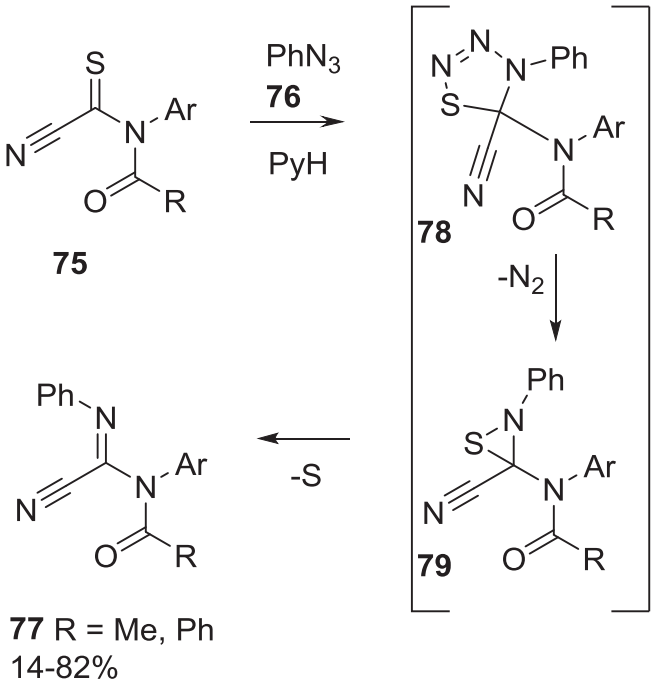
Amidines. Cyanothioformamides **75** were combined with phenyl azide **76** to afford amidines **77** as the final products; the process is postulated to be accompanied with elimination of N_2 and S from

thiatriazole **78** and thiaziridine **79** intermediates (Scheme 22) [62]. Presumably, as in the reaction with diazo compounds (*cf.* Scheme 4), the cyano group attached to the thioamide group activates the C=S bond for the cycloaddition with 1,3-dipoles.

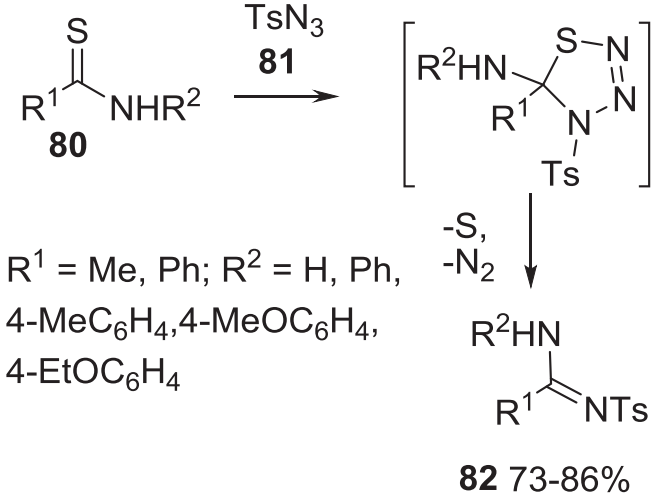
However, this novel reaction remains the only example of formation of amidines from the reaction of thioamides with aryl azides. In contrast to aromatic azides, the highly electrophilic sulfonyl azides were shown by Zelenskaya *et al.* [63] and other groups following up on this report [64–69] to be more prone to react with thioamides to form *N*-sulfonyl amidines. Thus Zelenskaya *et al.* discovered that thioamides of acetic and benzoic acid **80** reacted with tosyl azide **81** in pyridine to form *N*-tosylamidines **82** in 73–86% yields (Scheme 23) [63].

The Chiba group has found that the reaction proceeds also in water, alcohols and other polar solvents [65,66]. Protic solvents, ethanol and water gave the best results. The reaction has a wide scope; primary, secondary and tertiary thioamides **83** including cyclic ones react with mesyl- and benzenesulfonyl azides **84** to afford a variety of different *N*-sulfonyl amidines **85** in good to excellent yields (Scheme 24). It was shown that the reaction of thioamides of acetic acid (**83**, R^3 = Me) occurs faster than thiobenzamides (**83**, R^3 = Ph). Based on the fact that the reaction goes faster in polar than in apolar solvent and on calculation data for the energy and population of frontier orbitals, the author proposed a two-step mechanism for the formation of amidines **85** involving a thiatriazene intermediate.

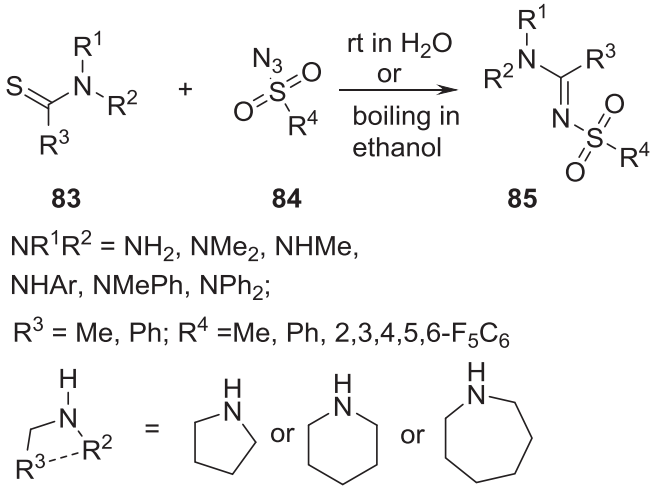
Further study of the reaction resulted in the development of a solvent-free protocol which was used by the Bakulev group for the successful synthesis of active methylene amidines **86a-d** from



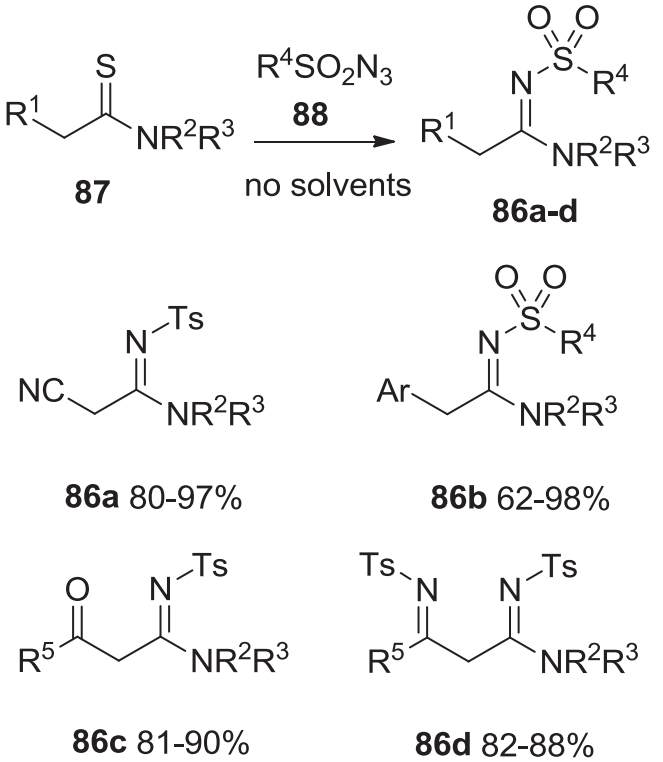
Scheme 22. Reaction of cyanothioamides **75** with azide **76**.



Scheme 23. Synthesis of amidines **82** [63].



Scheme 24. Synthesis of amidines **85** from reaction of thioamides **83** with sulfonyl azides **84**.

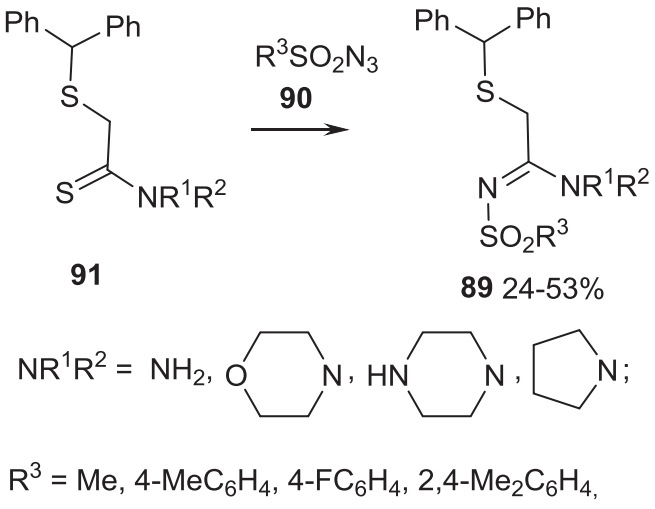


Scheme 25. Synthesis of active methylene amidines **86**.

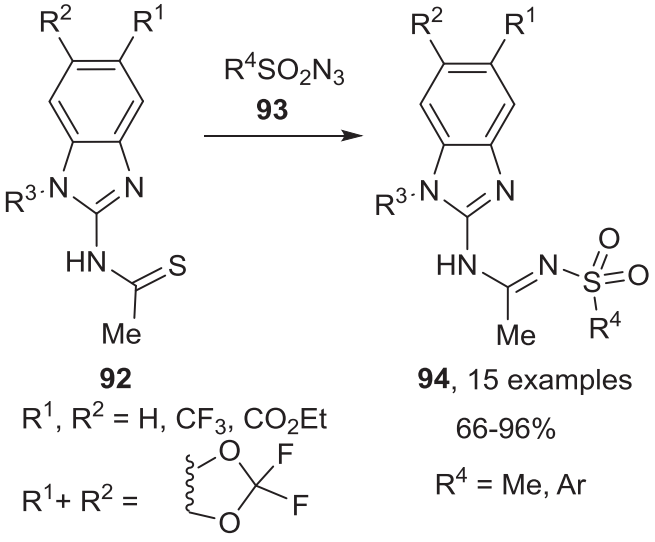
reaction of active methylene thioamides **87** with a variety of sulfonyl azides **88**. The absence of a solvent and the use of an equimolar amount of azide makes the protocol more eco-friendly (Scheme 25) [67].

The Bakulev and Lubec groups in cooperation applied this approach to the synthesis of *N*-sulfonylamidines of modafinic acid **89** which is a very effective inhibitor of dopamine transporter (Scheme 26) [68]. The scope of starting materials included a series of sulfonyl azides **90** and primary and tertiary thioamides of modafinic acid **91**. Here again, two general protocols were applied: (i) refluxing ethanol with 5 equivalents of an azide and (ii) neat, in solvent-free conditions with equimolar amount of an azide. The second variant was demonstrated to be more favorable, providing comparable yields in much shorter time and better economy in azide.

The reaction was further adapted to the synthesis of hybrid molecules comprising benzimidazole and *N*-sulfonyl amidine moieties, both known to impart biological activities of various types. In this specific application, the solvent-free protocol and the use of water as a solvent have failed. The reaction of thioamides **92** with azides **93** was found to be successful when a mixture of starting reagents in equimolar ratio was kept for 2–10 h in ethanol at reflux



Scheme 26. Synthesis of *N*-sulfonylamidines of modafinic acid **89**.



Scheme 27. Synthesis of *N*-sulfonyl amidine **94**.

to form amidines **94** (Scheme 27) [69]. It was shown that sulfonyl azides **93** did not react with thioamides **92** (R = CF_3) in any of the applied conditions.

In *conclusion*, contrary to thioketones, thioamides, due to 'thioamide resonance', are much less active in reactions with dipoles. Exceptions from this rule are thioamides of cyanoformic acid, which easily react with diazo compounds and azides at room temperature resulting in amidines and their vinylogs, enamines. Developments in synthetic methods based on the reactions under consideration included the use of sulfonyl azides in preparation of *N*-sulfonyl amidines and introduction of ruthenium- and copper-containing catalysts in the synthesis of enamines. The use of rhodium-containing catalysts in the reaction of diazo compounds with thioamides affords various heterocyclic compounds, such as mono- and bicyclic thiophenes, thioisomunchnones, thiazoles, and benzothiazines. Application of another type of catalysts, Lewis acids, in reaction of thioamides with inorganic azides gave impetus to progress in the preparative chemistry of tetrazoles. Further advance in synthetic possibilities of reactions of thioamides with diazo compounds and azides could be achieved after theoretical investigations of the high reactivity of thioamides of cyanoformic acid towards dipolar compounds and the unique capability of sulfonyl azides to react with thioamides to form amidines.

Acknowledgement

The authors thank the Russian Scientific Foundation for financial support (grant 18-13-00161).

References

[1] M. Shekarchi, M. Pirali-Hamedani, L. Navidpour, N. Adib, A. Shafiee, J. Iran. Chem. Soc. 5 (2008) 150.
[2] M.S. Chernovyants, N.V. Aleshina, J. Anal. Chem. 67 (2012) 214.
[3] G.J. Corban, S.K. Hadjikakou, A.C. Tsipis, M. Kubicki, T. Bakas, N. Hadjiliadis, New J. Chem. 35 (2011) 213.
[4] R. Kulandasamy, A.V. Adhikari, J.P. Stables, Bull. Korean Chem. Soc. 31 (2010) 3318.
[5] S. Ravez, C. Corbet, Q. Spillier, A. Dutu, A.D. Robin, E. Mullarky, L.C. Cantley, O. Feron, R. Frédérick, J. Med. Chem. 60 (2017) 1591.
[6] T.S. Jagodzinski, Chem. Rev. 103 (2003) 197.
[7] V.D. Dyachenko, I.V. Dyachenko, V.G. Nenajdenko, Rus. Chem. Rev. 87 (2018) 1.
[8] A. Yoshimura, A.D. Todora, B.J. Kastern, S.R. Koski, V.V. Zhdankin, Eur. J. Org. Chem. (2014) 5149.
[9] N.P. Belskaia, T.G. Deryabina, A.V. Koksharov, M.I. Kodess, W. Dehaen, A.T. Lebedev, V.A. Bakulev, Tetrahedron Lett. 48 (2007) 9128.
[10] (a) O.M. Ghoneim, A. Bill, J. Dhuguru, D.E. Szollosi, I.O. Edafiogho, Bioorg. Med. Chem. 26 (2018) 3890;
(b) G.V. Boyd, Chemistry of Amidines and Imidates, Wiley, New York, 1991, p. 8.3, Chapter 8.3;
(c) B. Zhao, K. Qian, X. Nan, L. Yang, X. Yang, H. Hung, J. Yang, D. Kuo, M. Goto, S. Morris-Natschke, S. Pan, C. Teng, S. Kuo, T. Wu, Y. Wu, K. Lee, J. Med. Chem. 57 (2014) 6008.
[11] (a) J.W. Scheeren, P.H.J. Ooms, R.J.F. Nivard, Synthesis (1973) 149;
(b) J. Bergman, B. Pettersson, V. Hasimbegovic, P.H. Svensson, J. Org. Chem. 76 (2011) 1546;
(c) T.J. Curphey, J. Org. Chem. 67 (2002) 6461;
(d) U. Pathak, L.K. Pandey, R. Tank, J. Org. Chem. 73 (2008) 2890;
(e) M. Jesberger, T.P. Davis, L. Barner, Synthesis 2003 (1929) 13;
(f) X.-T. Cao, L. Qiao, H. Zheng, H.-Y. Yang, P.-F. Zhang, RSC Adv. 8 (2018) 170;
(g) J.K. Lie, Name Reactions, Springer, Cham, Switzerland, 2014, p. 629;
(h) I.S. Fedorovich, N.I. Ganushchak, V.V. Karpyak, N.D. Obushchak, A.I. Lesyuk, Rus. J. Org. Chem. 43 (2007) 1190;
(i) L. Liu, Z. Guo, K. Xu, S. Hui, X. Zhao, Y. Wu, Org. Chem. Front. 5 (2018) 3315;
(j) K. Okamoto, T. Yamamoto, T. Kanbara, Synlett (2007) 2687;
(k) S.P. Pathare, P.S. Chaudhari, K.G. Akamanchi, Appl. Catal. A: Gen. 425–426 (2012) 125.
[12] G. Mloston, H. Heimgartner, in: The Chemistry of Heterocyclic Compounds. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Wiley, New York, 2002, p. 360.
[13] G. Mloston, H. Heimgartner, Pol. J. Chem. 74 (2000) 1503.
[14] G. Mloston, H. Heimgartner, Curr. Org. Chem. 15 (2011) 675.
[15] V.A. Nikolaev, A.V. Ivanov, L.L. Rodina, G. Beilst Mlostoń, J. Org. Chem. 9 (2013) 2751.
[16] D.H. Egli, A. Linden, H. Heimgartner, Helv. Chim. Act. 2006 (1910) 89.
[17] D.H. Egli, A. Linden, H. Heimgartner, Helv. Chim. Act. 90 (2007) 86.

[18] H.-S. Kim, I.-C. Kwon, O.-H.J. Kim, Het. Chem. 32 (1995) 937.
[19] A.M.Sh. Al-Sharief, Z. Moussa, Eur. J. Med. Chem. (2009) 4315.
[20] X. Fontrodona, S. Diaz, A. Linden, J.M. Villalgordo, Synthesis (2001) 2021.
[21] B. Shi, W. Lewis, I.B. Campbell, C.J. Moody, Org. Lett. 11 (2009) 3686.
[22] M.A. Honey, R. Pasceri, W. Lewis, C.J. Moody, J. Org. Chem. 77 (2012) 1396.
[23] C.J. Moody, A.M.Z. Slawin, D. Willows, Org. Biomol. Chem. 1 (2003) 2716.
[24] B.V.S. Reddy, R.A. Babu, M.R. Reddy, B.J.M. Reddy, B. Sridhar, RSC Adv. 4 (2014) 44629.
[25] Yu. Yu. Medvedev, I.V. Efimov, Yu. M. Shafran, V.V. Suslonov, V.A. Bakulev, V.A. Nikolaev, Beilstein J. Org. Chem. 13 (2017) 2569.
[26] G. Kim, M.Y.C. Moyer, S.J. Danishefsky, G.K. Schulte, J. Am. Chem. Soc. 115 (1993) 30.
[27] A. Padwa, F.R. Kinder, W.R. Nadler, L. Zhi, Heterocycles 35 (1993) 367.
[28] H. Nakano, T. Ishibashi, T. Sawada, Tetrahedron Lett. 44 (2003) 4175.
[29] N.D. Koduri, H. Scott, B. Hileman, J.D. Cox, M. Coffin, L. Glicksberg, S.R. Hussaini, Org. Lett. 14 (2012) 440.
[30] N.D. Koduri, Z. Wang, G. Cannell, R. Cooley, T.M. Lemma, K. Miao, M. Nguen, B. Frohock, M. Castaneda, H. Scott, D. Albinescu, S.R. Hussaini, J. Org. Chem. 79 (2014) 7405.
[31] S.R. Hussaini, R.R. Chamala, Z. Wang, Tetrahedron 71 (2015) 6017.
[32] L. Mohammadi, M.A. Zolfigol, M. Ebriminia, K.P. Roberts, S. Ansari, T. Azadbakht, S.R. Hussain, Cat. Comm. 102 (2017) 45.
[33] A. Pal, N.D. Koduri, Z. Wang, E.L. Quiroz, A. Chong, M. Vuong, N. Rajagopal, M. Nguyen, K.P. Roberts, S.R. Hussaini, Tetrahedron Lett. 58 (2017) 902.
[34] V.A. Bakulev, W. Dehaen, The Chemistry of 1,2,3-Thiadiazoles, John Wiley & Sons Inc, USA, 2004.
[35] Y. Shafran, T. Glukhareva, W. Dehaen, Adv. Heterocycl. Chem. 126 (2018) 109.
[36] V.A. Bakulev, Y.Y. Morzherin, A.T. Lebedev, E.F. Dankova, M.Y. Kolobov, Y.M. Shafran, Bull. Soc. Chem. Belg. 102 (1993) 493.
[37] W.M.F. Fabian, V.A. Bakulev, C.O. Kappe, J. Org. Chem. 63 (1998) 5801, and references herein.
[38] M.S. Singh, A. Nagaraju, G.K. Verma, G. Shukla, R.K. Verma, A. Srivastava, K. Raghuvanshi, Green Chem. 15 (2013) 954.
[39] T.V. Glukhareva, Yu.Yu. Morzherin, L.V. Dyudya, K.V. Malysheva, A.V. Tkachev, A. Padwa, V.A. Bakulev, Russ. Chem. Bull. 53 (2004) 1311.
[40] P.E. Prokhorova, T.V. Glukhareva, L.V. Dyudya, E.A. Alekseeva, Yu.Yu. Morzherin, Russ. Chem. Bull. 59 (2010) 867–869.
[41] T.A. Kalinina, P.E. Prokhorova, T.V. Glukhareva, Yu.Yu. Morzherin, Russ. Chem. Bull. 60 (2011) 981.
[42] V.O. Filimonov, L.N. Dianova, K.A. Galata, T.V. Beryozkina, M.S. Novikov, V.S. Berseneva, O.S. Eltsov, A.T. Lebedev, P.A. Slepukhin, V.A. Bakulev, J. Org. Chem. 82 (2017) 4056.
[43] L.N. Dianova, V.S. Berseneva, O.S. El'tsov, Z.-J. Fan, V.A. Bakulev, Chem. Het. Compd. 50 (2014) 972.
[44] N.A. Belyaev, T.V. Beryozkina, V.A. Bakulev, Tetrahedron Lett. 52 (2016) 206.
[45] P.E. Kropotina, L.V. Dyudya, T.V. Glukhareva, Yu. Yu. Morzherin, V.A. Bakulev, K.V. Hecke, L.V. Meervelt, W. Dehaen, Mendeleev Commun. 16 (2006) 76.
[46] D. Kurandina, V. Gevorgyan, Org. Lett. 2016 (1804) 18.
[47] J.-Y. Son, J. Kim, S.H. Han, S.H. Kim, P.H. Lee, Org. Lett. 18 (2016) 5408.
[48] J.E. Kim, J. Lee, H. Yun, Y. Baek, P.H. Lee, J. Org. Chem. 82 (2017) 1437.
[49] B. Seo, H. Kim, Y.G. Kim, Y. Baek, K. Um, P.H. Lee, J. Org. Chem. 82 (2017) 10574.
[50] A.-A.S. El-Ahl, F.A. Amer, A.H. Elbeheery, Phosph. Sulfur, Silicon Relat. El. 186 (2011) 2226.
[51] C.M. Athanassopoulos, T. Garnelis, D. Vahliotis, D. Papaioannou, Org. Lett. 7 (2005) 561.
[52] M. Koufaki, C. Kiziridi, F. Nikoloudaki, M.N. Alexis, Bioorg. Med. Chem. Lett. 17 (2007) 4223.
[53] M. Koufaki, E. Theodorou, X. Alexi, M.N. Alexis, Bioorg. Med. Chem. 18 (2010) 3898.
[54] M. Koufaki, C. Kiziridi, X. Alexi, M.N. Alexis, Bioorg. Med. Chem. 17 (2009) 6432.
[55] D.W. Nelson, R.J. Gregg, M.E. Kort, A. Perez-Medrano, E.A. Voight, Y. Wang, G. Grayson, M.T. Namovic, D.L. Donnelly-Roberts, W. Niforatos, P. Honore, M.F. Jarvis, C.R. Faltynek, W.A. Carroll, J. Med. Chem. 49 (2006) 3659.
[56] Abbott Laboratories. WO Patent 86 229, 2006.
[57] S. Thompson, A. Venkatesan, T. Priestley, M. Kundu, A. Saha, WO Patent 95 128, 2015.
[58] F. Lv, Z.-F. Li, W. Hu, X. Wu, Bioorg. Med. Chem. 23 (2015) 7661.
[59] Nissan Chemical Industries, Ltd. WO Patent 57 827, 2009.
[60] S.J. Charlton, C. Leblanc, S.C. McKeown, O Patent 105 063, 2013.
[61] W.M. Abdou, N.A. Ganoub, E. Beilst Sabry, J. Org. Chem. 9 (2013) 1730.
[62] K. Friedrich, M. Zamkanei, Chem. Ber. 1979 (1873) 112.
[63] O.V. Zelenskaya, V.A. Kozinsky, A.V. Nazarenko, A.P. Ransky, J. Appl. Chem. 57 (1984) 1071.
[64] Y. Hatanaka, J. Chiba, T. Tomohiro, Japan Patent 6 112 659, 2017.
[65] M. Aswad, J. Chiba, T. Tomohiro, Y. Hatanaka, Chem. Comm. 49 (2013) 10242.
[66] M. Aswad, J. Chiba, T. Tomohiro, Y. Hatanaka, Tetrahedron Lett. 57 (2016) 1313.
[67] L. Dianova, V. Berseneva, T. Beryozkina, I. Efimov, M. Kosterina, O. Eltsov, W. Dehaen, V. Bakulev, Eur. J. Org. Chem. (2015) 6917.
[68] T. Beryozkina, V. Bakulev, L. Dianova, V. Berseneva, P. Slepukhin, J. Leban, P. Kalaba, N.Y. Aher, M. Ilic, H.H. Sitte, G. Lubec, Synthesis 48 (2016) 1046.
[69] N.A. Rupakova, V.A. Bakulev, U. Knippschild, B. García-Reyes, O.S. Eltsov, G.P. Slesarev, N.A. Beliaev, P.A. Slepukhin, L. Witt, C. Peifer, T.V. Beryozkina, Arkivoc 3 (2017) 225.